

Delivery Vehicle for Rapid Low-Cost Medical Infectious Disease Diagnostic

Tests: Portable Paper Diagnostic Dispenser for Developing Countries

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Shi, Marlene. Infectious diseases still plague much of the developing world. Rapid and accurate diagnosis of diseases such as malaria, tuberculosis, and HIV is critical for improved control and management allowing for targeted and effective treatment. The Whitesides Research Group led by George Whitesides, the Woodford L. and Ann A. Flowers University Professor at Harvard, has developed a low-cost paper based diagnostic test that follows the principles of microfluidics using paper's inherent channels and natural capillary action.

The first application that the Whitesides paper diagnostic test will perform is liver toxicity screening. The printing method for these diagnostic tests will model the newspaper press print format for efficient and speedy production. The Whitesides Group intends the test results to be analyzed using telemedicine. Camera phones will transmit images of the test to a lab where a doctor or a computer can make a diagnosis.

The key area that has not yet been explicitly defined is the method of packaging, distribution, and portability of the paper diagnostic test squares. The proposed paper diagnostic dispenser will make the tests portable which will increase access to diagnostic tools in the developing world. Health care volunteers will be able to carry the tests in a simple container and dispense test squares as needed. This device increases the mobility of health care workers, requires little to no training to use, and

facilitates the decentralization of health care services in developing countries.

INTRODUCTION

Problem: The need for standard diagnostics

Despite successes in smallpox and polio eradication, age-old infectious diseases have yet to become obsolete. Historic diseases such as malaria and tuberculosis still plague much of the developing world. The World Health Organization (WHO) promotes global health initiatives, and infectious diseases have always been the top priority [15]. Progress in eradicating infectious diseases is particularly measureable in terms of prevention, control, treatment, and cure [15].

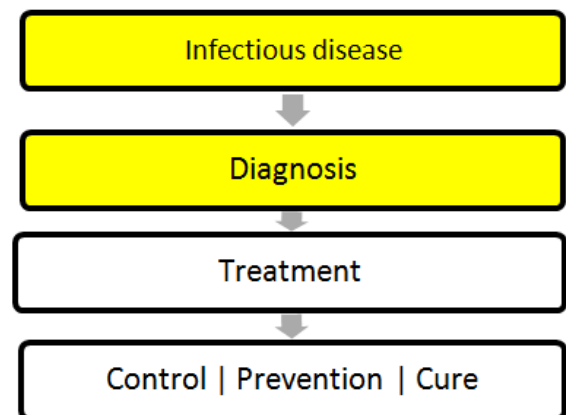


Fig. 1 The pathway leading to the eradication of infectious disease. Diagnosis is a key step that allows for effective treatment and management of the disease.

Current studies reveal that malaria, HIV, and tuberculosis are still leading

contributors of mortality in developing countries. Over 95% of these deaths are caused by the lack of proper diagnosis and treatment, yet the standard diagnostic techniques listed in Fig. 2 below are costly, slow, and limited in sensitivity to different pathogens [10].

Given this startling statistic, there is a clear need to develop diagnostic devices for countries where access to adequate health care infrastructure is limited. New advanced medical technology is being produced such as lab-on-a chip devices. However common platforms made of glass or other forms with sensors are expensive and for a developing country – cost as well as cost effectiveness determine health care decisions.

Case study I. Malaria

Fever, chills and vomiting are common symptoms at the onset of malaria,

but when mild these symptoms do not clearly indicate infection [18]. Rapid and accurate diagnosis is critical because malaria can progress to severe illness after 24 hours of infection [18]. In 2009, malaria was the cause of over one million deaths worldwide [18]. In Africa one child dies every 45 seconds of malaria [18].

In a public health study conducted in the tribal belt of Central India where there is a high prevalence of malaria, researchers found that the local natives must travel several hours, even days, to get to a lab facility for malaria diagnosis via microscopy, the gold standard diagnosis method [1]. However, microscopy requires trained lab technicians, a reliable power supply, and materials for sample preparations [1]. Thus, some results are not available until four to six weeks later [1]. The delayed diagnosis further delays treatment and enables transmission [1]. When access to primary

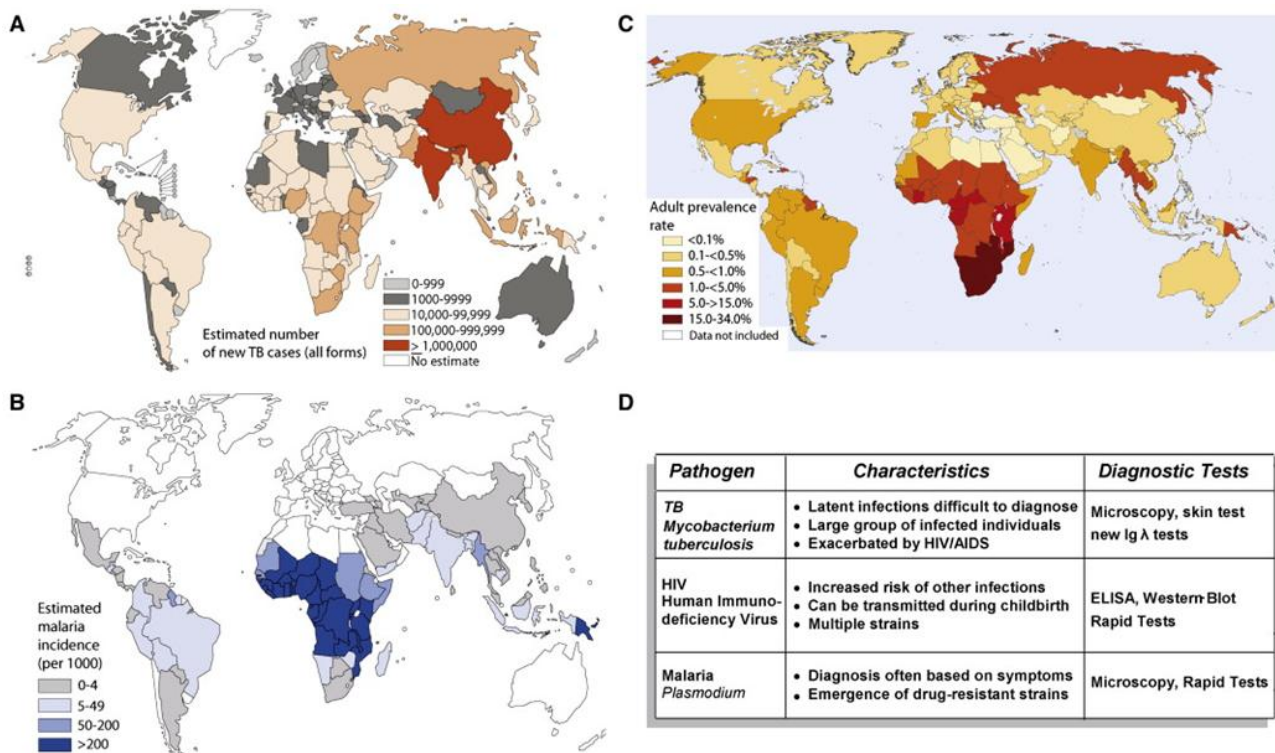


Fig. 2 Distribution of HIV, tuberculosis and malaria in the world. These diseases have particularly high incidence rates and prevalence in developing regions such as Africa and Southeast Asia. Maps adapted from the World Health Organization. (A) Estimated TB incidence rates, by country, 2007. (B) Estimated incidence of malaria per 1000 population, 2006. (C) A global view of HIV infection (39.5 million people [34.1-47.1] living with HIV in 2006). (D) Key diseases and specific concerns associated with these diseases. Of note, rapid tests refer to the immunochromatographic method or the dipstick test. [1]

health centers with trained microscopists is limited or unavailable, diagnosis of malaria is often made based on clinical symptoms, but this method is at best 50% accurate giving false positives that waste medication and lead to drug-induced side effects [19].

Misdiagnosis leads to the improper use of anti-malarial drugs, which wastes treatment resources and can cause unexpected side effects [9]. On the other hand, untreated malaria leads to severe illness and eventual death. Countries with high prevalence of malaria suffer high economic losses – as much as a 1.3% decrease in gross domestic product (GDP) [18]. Therefore, there is a clear need for low-cost, portable, rapid diagnostic screening tools in developing countries, especially rural areas with logistical and financial constraints.

Case study II. HIV

Currently over 40 million people are infected with HIV with 96% living in developing countries [16]. Sub-Saharan Africa has the highest number of cases [16].

In a study focused on the access to diagnostics in support of HIV/AIDS and tuberculosis treatment in developing countries, it was found that 90% of those living with HIV are unaware of their condition because they were never tested [3]. The large population of people living with HIV without their knowledge is a significant contributor to the transmission of HIV.

Experienced lab technicians are limited in developing countries, thus

effectively operating labs that can perform standard diagnostic tests are sparse. Furthermore, having a centralized health care center in developing countries is not practical when there are many rural communities with citizens that do not have access to transportation.

While there are available low-cost and rapid HIV tests, these diagnostics are not being deployed [3]. Thus a method of deployment is necessary. The portable paper dispenser is one solution that could increase the deployment of diagnostic tests and enable global volunteers to administer more tests so that HIV patients are aware that they have the disease and prevent continued transmission.

Case study III. Tuberculosis

As much as one-third of the world's population is estimated to have tuberculosis – mostly the latent form [3]. 15 million currently live with an active form of TB with 9 million new cases per year [3]. New cases of TB have risen in recent years due to HIV. TB causes 2 million deaths per year [3].

Despite the prevalence of TB, most of the developing countries are relying on 115 year old acid-fast bacillus sputum smear tests [3]. Sensitivity is poor to begin with and it is even more difficult to accurately diagnose patients with HIV raising false negative results [3].

Other limitations of sputum smears are that they are difficult to use with

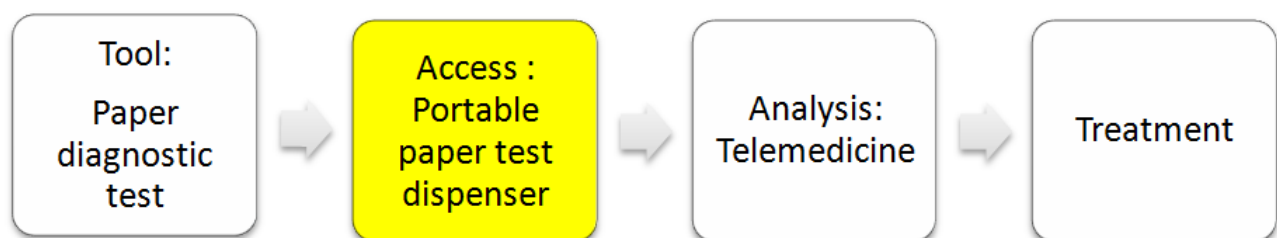


Fig. 3 Deployment of diagnostic tests.

children and that analysis requires microscopes and trained lab technicians [3]. Thus current diagnostic tests used to detect TB are not only poor in accuracy but limited in mobility. A low-cost portable paper test is an ideal solution to improve TB diagnosis.

ENGINEERING DESIGNS

Considerations and parameters

Developing countries are in great need of simple, portable, and effective infectious disease diagnostic devices that are cost effective. In 2009 the Gates Foundation announced a project to develop a standard platform for point-of-care diagnostic devices for the developing world because of concerns that less than 5% of deaths in developed nations are resulted from infectious disease whereas over 50% of deaths in many of the poorest regions are a result of infectious disease [8].

While most diagnostic tools are idiosyncratic, new initiatives are calling for open source standardized diagnostic tools that many companies can develop particular equipment and parts for. The Gates Foundation has committed to offering \$30 million in grants to developing such devices with the goal being easy-to-use devices that will not require advanced training or supplies [8]. One device being developed is a shoe-box-sized reader that analyzes samples such as blood, saliva or urine submitted on a microfluidic card [8]. Another device is being developed by Paul Yager, a bioengineering professor at the University of Washington. His device is nicknamed the DxBox and has the multifunction of performing polymerase chain reaction.

Given the great need for diagnostic tools that are suited for developing countries, the WHO has an established set of guidelines, ASSURED, to consider for new

inventions: (i) affordable, (ii) sensitive, (iii) specific, (iv) user-friendly, (v) rapid and robust, (vi) equipment-free, and (vii) delivery to those who need it [11].

Deployment and mobility need

The important realization that transportation and accessibility to health care centers are limited in most developing countries has driven research towards the development of point-of-care (POC) diagnostics, which allows for convenient diagnosis on-site at the patient's location. The attractive characteristics of POC technology are concepts that can be implemented to create successful diagnostic tests for third world countries: disposability, cost-effectiveness, ease of use and portability [5].

To reduce the cost of diagnostics the following cost-effective measures can be implemented: minimal use of expensive reagents, inexpensive manufacturing for mass production, quality control, and miniaturization [13]. Other parameters that must be accounted for in devices for developing countries include streamlining the steps of use (i.e. eliminating menial intermediate steps such as cutting paper strips or washing processes) and environmental conditions, which broadly encompasses sensitivity to high temperatures, humidity, and inadequate water and electricity access [2].

Infectious diseases are a challenging health issue globally, particularly for developing countries with limited resources and environmental barriers to overcome. Countless studies have identified the specific need for improvement in the diagnosis of infectious diseases. Better diagnostic devices would improve the diagnosis of major diseases such as malaria, tuberculosis, and HIV. Faster and more accurate diagnosis has the potential to save

millions of lives and allow for better treatment and prevention while reducing the number of misdiagnosis. The Gates Foundation lists a syphilis detection diagnosis medical device as a tool that has the potential to prevent 215,000 stillbirths, and a standardized malaria test can save more than 2 million lives and prevent 450 million unnecessary treatments due to misdiagnosis per year [8].

SOLUTION

The identified public health problem is the need for accurate, low-cost, accessible diagnostic tests for infectious diseases – namely malaria, HIV, and tuberculosis. While these tests do exist particularly with the development of paper-based diagnostics, an easy method of transport and use of the tests is needed to conveniently utilize the diagnostic tests. The next step is commercialization and dissemination.

The portable paper diagnostic test dispenser is designed to be compatible with the Whitesides paper design. Whitesides has co-founded a nonprofit organization Diagnostics for All (DFA) for commercialization purposes. DFA plans to deploy the first tests to sub-Saharan Africa in the fall of 2010. The first tests will test for liver toxicity.

Stage I. Low-cost paper diagnostic test

The first step in the overall process is to create an ASSURED diagnostic device that meets the additional design considerations such as disposability and low cost. Paper diagnostic tests are an ideal solution because expensive sensors and analyzers, external pumps, and power sources are eliminated. Paper diagnostics relies on the paper's natural capillary action of liquid absorption and the inherent channels in patterned paper, which make

paper an ideal medium for chemical reactions.

Diagnostic tests made out of paper are a low cost solution that meets the ASSURED criteria. Paper has various advantages over its plastic and glass counterparts and has been the recent focus of various researchers including Dr. George Whitesides of Harvard University. The following advantages of paper tests were listed in a recent paper published by members of the Whitesides Lab, who used Whatman No. 1 chromatography paper: thin (0.07 – 1 mm), lightweight ($\sim 10 \text{ mg/cm}^2$), easy packaging and transport, compatible with biological samples, good medium for colorimetric tests, disposable by incineration, flexible and compatible with various printing technologies for simple fabrication, low cost and easily modified chemically [12]. Furthermore, these tests eliminate sharps waste, which is ideal for developing countries and significantly simplifies a relatively untrained health care volunteer's task [17]. Needle disposal concerns are eliminated because the paper tests require only very small amounts of fluid.

The current paper diagnostic tests developed have shown efficiency in that multiple tests can be performed on the same small 2 cm x 2 cm square as shown in Fig. 4.



Fig. 4: Three - branched tree with two testing wells for glucose and protein assays [6].

Rapid results appear ranging from 5 – 30 minutes depending on the specific test. Furthermore, mass production using

newspaper print technology drives down the cost of this device to \$0.03 - \$0.05 making paper diagnostics a realizable tool for detecting infectious diseases in developing countries [6].

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Stage II. Packaging and deployment

Now that cost effective paper diagnostic tools have been developed, there is a need for an efficient vehicle with which to package, transport, and deliver the tests to the populations in need. The proposed solution is a paper diagnostic dispenser based upon the simple tape dispenser concept with a few minor alterations: (i) casing will completely enclose internal wheel and test strips except for the one being dispensed, (ii) ratchet mechanism to allow for an exact dispense length, (iii) color code will be printed on the casing surface for easy reference.

Detailed design schematics

The final built prototype consists of 3 separate pieces: top and bottom casing shells and a freely-rotating spool. Additional added components include a spring and nail for the allotted dispense mechanism.

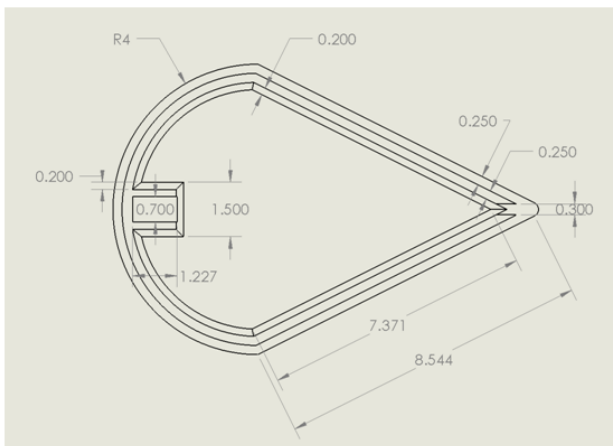


Fig. 5: Top half case measurements. The housing structure seen along the curved circumference of the case is meant to store a spare spring

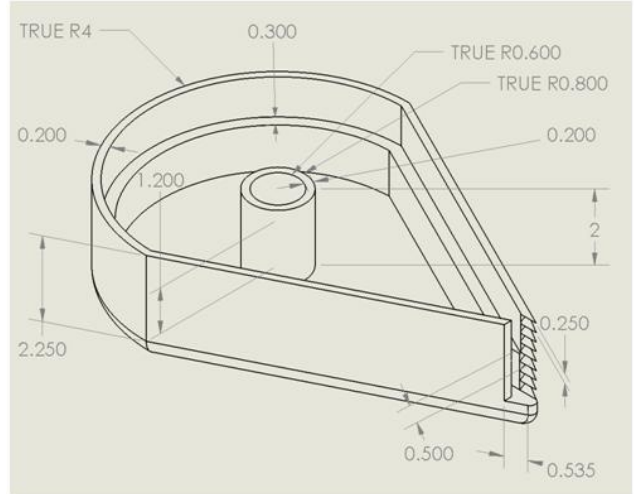


Fig. 6: Bottom half casing.

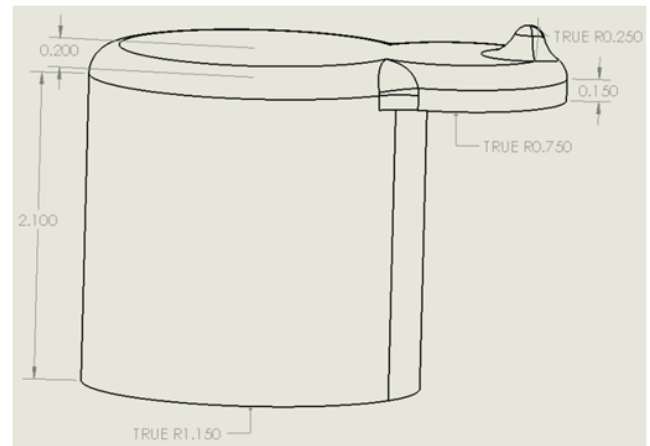


Fig. 7: Spool cap.

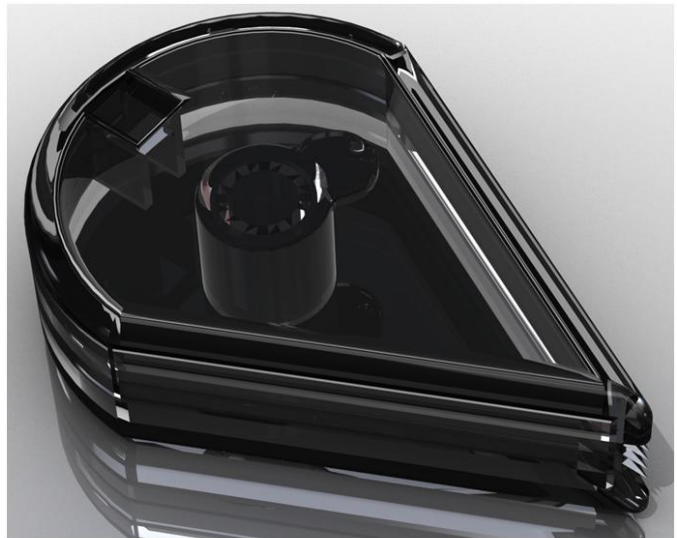


Fig. 8: Final built prototype image.

Stage III. Telemedicine

The final components of the system involve diagnosis and treatment. With the portable paper dispenser and the rapid results given by paper tests developed by the Whitesides Group, it is possible for medical volunteers to travel to remote locations, administer diagnostic tests, and give a general on-spot diagnosis with the color code printed on the dispenser casing. This will be useful in providing information quickly, but the treatment does not stop there. The results of the paper diagnostic need to be sent to a central lab where trained health care workers can analyze the information and prescribe a specific diagnosis and treatment.

Telemedicine is a viable solution in remote settings. Mobile volunteers should be equipped with a camera phone. Following the appearance of results on paper tests, the worker will proceed to take a picture of the test and transmit the information to a central lab. This approach is efficient and allows for developing countries to access experts who under normal circumstances may not have the time to travel to distant or remote locations [12].

RESULTS

The portable dispenser achieves several of the initial design goals. The tape analogy allows for the diagnostic tests to be efficiently packaged in the designed casing. The dispensing mechanism of the first prototype consistently allots 9cm per pull. The prototype consists of three separate parts: top and bottom casing and a free-rotating spool. The hook spring allows for consistent test dispense and the nail is an attachment peg for the spring. The teeth In consideration of mass production, this device will ultimately be extremely low-cost. Based on comparable everyday plastic tape

dispensers, an estimate of the portable diagnostic dispenser cost is somewhere under \$0.50 to produce with the spring component as the most expensive item.

Testing

The portable dispenser has undergone durability testing. The device has been found to have structural integrity surviving multiple drops onto a hard linoleum surface as well as 200N of exerted force pressing the case as well as pulling the tape.

The Whitesides Group has tested the paper diagnostics and the results of the colorimetric tests can be seen in the figure below.

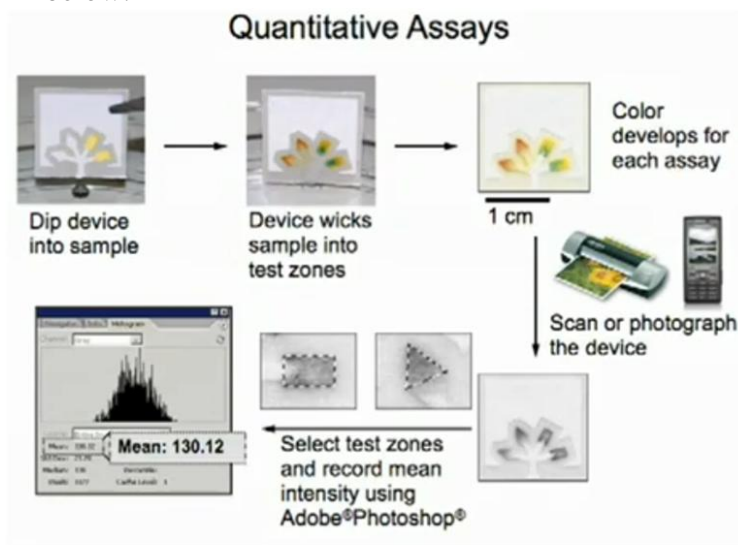


Fig. 9: Paper diagnostic tests can be easily implemented in developing countries [17].

Future direction

Future testing will be conducted. The first deployment of the paper diagnostic tests is expected to occur in the fall of 2010. Liver toxicity tests will be used in sub-Saharan Africa where much of the population is inflicted with HIV. HIV treatment drugs have harsh side effects especially to the liver [17]. Deployment of the test square will also

allow for a better analysis of environmental impact on the tests.

Following a conversation with a graduate student in Dr. Jeff Wang's lab, one future direction that should be explored is to create a color patch for the diagnostic tests and a color correction program that can properly calibrate the colors for greater accuracy when interpreting results. The inventors of the paper diagnostic test also recognize the distortion of color images transmitted that could arise due to variable intensity based on lighting conditions, resolution of camera and focus of picture [12]. Printing a color patch onto the paper test that could be read by a program is one potential solution that can account for the variable conditions.

Another project direction would be to create a device to hold and dispose paper tests after they have been administered. The portable paper dispenser is a method for transporting new diagnostic tests, but after samples have been collected there is a need for a container to hold the paper tests for later disposal. There is also further work to be done to create more advanced paper tests that can diagnose infectious diseases such as HIV with greater accuracy.

As Whitesides said himself at the 2010 TED conference, "a health care worker of the future is not a doctor, but an 18 year-old otherwise unemployed who has two things: a backpack full of these tests and a lancet to occasionally take a blood sample – and an AK-47" [17].

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APPENDIX

Design iterations

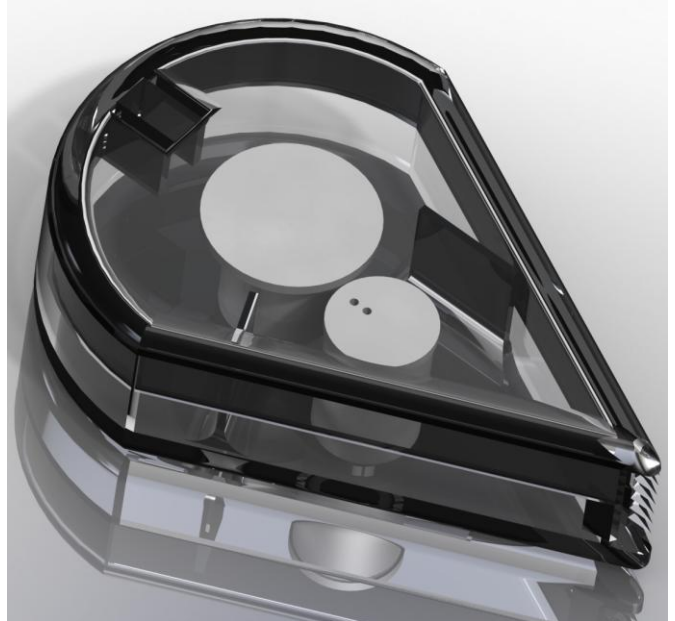


Fig.10: Two-spool ratchet mechanism.



Fig. 11: Ratchet wheel spool design.